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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
WEGERT, SANDRA L

ART UNIT	PAPER NUMBER
1647	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/024,535	MARCEL ET AL.	
	Examiner	Art Unit	
	Sandra Wegert	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 February 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,15-17,22 and 51-59* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,15-17,22 and 51-59* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 December 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/13/06, 2/8/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments, and/or Claims

The Remarks/Arguments, and Information Disclosure Statement, submitted 13 November 2006, have been entered and considered. Claims 1, 51 and 59 were amended. The Information Disclosure Statement, submitted 8 February 2007, has been entered and considered. Claims 1, 15-17, 22 and 51-59 are under examination as well as the following secondary Inventions: SEQ ID NO: 2 and *impaired social activity linked to sexuality*.

Non-elected species of sexual behaviors will remain withdrawn, pending an indication of allowable subject matter (*In re Ochiai, In re Brouwer* and 35 U.S.C. § 103(b), 1184 O.G. 86 March 26, 1996). Claims that encompass elected and non-elected subject matter are being examined in this Office Action.

Withdrawn Objections and/or Rejections

Claim Objections -

The objection to Claim 59 for encompassing non-elected inventions (such as mental disorders not related to *impaired social activity related to sexuality*) is withdrawn. Applicants amended Claim 59 to recite only the elected invention (13 November 2006).

Claim rejections- 35 USC § 112, first paragraph-Written Description

The rejection of Claims 1, 15-17, 22 and 51-59 under 35 U.S.C. 112, first paragraph, for lack of Written description is *withdrawn*, based on Applicants' arguments (13 November 2006).

Maintained/New Objections and/or Rejections

Claim Objections -

The objection to Claim 1 for encompassing non-elected inventions is *maintained*. Claim 1 recites a method for treating a "mental disorder" which includes mental disorders not related to the elected invention of *impaired social activity related to sexuality*.

Appropriate correction is required.

Claim Rejections- 35 USC § 112, first paragraph-Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> **The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.**

Claims 1, 15-17, 22 and 51-59 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The specification is not enabling for a method of administering the SMR1 peptide of SEQ ID NO: 2 in order to treat a mental disorder, or a disorder such as *impaired social activity linked to sexuality*. The reasons for this rejection were given in the previous Office Actions (the most recent being 11 July 2006).

Claims 1, 15-17, 22 and 51-59 are drawn to a method of treating a mental disorder in a mammal in need thereof, by administering the short peptide of SEQ ID NO: 2 to a mammal.

Dependent claims define the mental disorder specifically as *impaired social activity linked to sexuality.* Additional dependent claims recite several disorders of sexual behavior and several routes of drug administration.

Experiments were described in the specification in which the FG-005 peptide of SEQ ID NO: 2 was administered intravenously, at doses of 3-30μg/kg, to *normal* male rats. Data were collected on the general alertness and insensitivity to pain of the treated animals. The Specification also describes experiments in which the effect of the peptide was measured in a test of anxiety: the forced swim test (page 26, instant Specification), with the FG-005 peptide acting like an anxiolytic. Several experiments also report the frequency and duration of several sexual behaviors when peptide-treated male rats were presented with female rats. Treated rats behaved as if they had been given an anxiolytic such as a benzodiazepine or ethanol, or a selective serotonin reuptake inhibitor, such as fluoxetine (Pfaus, et al, 2003, Annual Review of Sex Research, 14:1-63, see p. 16; Islam, 1991, J. Ethnopharmacol., 33: 67-72, see p. 71. Both papers of record). For example, male rats were reluctant to mount a female rat initially- but had more mounts subsequently (see Tables I-VI, Specification). The treated male rats also mounted the female more times before ejaculation, and mounted her more often during refractory periods, without ejaculation, than untreated rats.

A sufficient amount of direction or guidance is lacking in claims 1, 15-17, 22 and 51-59. The specification describes the intravenous administration of SEQ ID NO: 2 and the measurement of the duration and frequency of several rat sexual behaviors. However, nowhere in the specification is a method described that can be considered a treatment of a mental disease

including *impaired social activity linked to sexuality,* as applied to humans or other mammals. Nowhere in the instant Disclosure is a nexus described between the behaviors caused by (or inhibited by) SEQ ID NO: 2, and a well-defined disorder in human beings. Nor does current or prior literature suggest actual mental disorders that might be treated with the peptide of SEQ ID NO: 2. The applicants cite the DSM-IV diagnostic criteria associated with a hypoactive sexual desire disorder (Response, 19 April 2006, page 7) stating that such a disorder causes marked distress. As the examiner has argued repeatedly in prior Office Actions, the diagnostic criteria as put forth in the DSM-IV (American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition. Washington, DC, American Psychiatric Association, 1994, section 302.71, pages 496-497) is *valid* for defining a sexual disorder. It, for example, makes the point that such a disorder is defined as a disorder *because* it causes distress in the patient. In fact, the examiner previously made the argument that it was this *lack* of distress that was one factor demonstrating that normal male rats cannot have a mental disorder related to sexual dysfunction (19 August 2005, page 6).

There were no animal models presented in the instant Specification that suggest mental disorders or disorders related to sexual behavior. The Specification defines such disorders as:

"As used herein, 'impaired social activity linked to sexuality' is impairment of social relationship to a sexual partner, which can lead to impairment of occupational functioning" (Specification, paragraph 54).

Applicants have submitted a paper by Pfaus, et al (2003, Annual Review of Sex Research, 14:1-63) to demonstrate that rats have appetitive sexual behaviors that could be described as having social components. The examiner agrees with the general thesis of Pfaus, et

al, that many aspects of rat sexual behavior can be studied and enumerated- and in great detail, apparently. The researchers' reasons for believing the rat is a good subject for sex research is that rats display a pattern of copulatory behavior that can be described as "opportunistic" (p. 10). In other words, normal rats can be described as generally uninhibited in their sexual behaviors, and will copulate "in a variety of circumstances, in dyads, triads, or large groups" and do not require privacy (e.g., from the observer/experimenter).

Pfaus, et al, also makes several points about how the rat is NOT a good model for some human behaviors. He states, for example, that most researchers use rats to study primarily the "neuroanatomy, neurochemistry, and pharmacology of sexual behavior" (bottom of page 50), and that: "at the level of the basic response 'rule' or physiological process we may be able to make logical and predictable jumps from animals to humans. At the level of emotional processing or outward expression of behavior, the rules may not be interchangeable" (p. 50).

Applicants insist that "one with skill in the relevant art would understand the meaning of 'impaired social activity" and 'linked to sexuality'" (Response, page 7). However, the terms must still be defined in the instant Specification, and the disorders to be treated by the SMR1 peptide must be *named*. The DSM-IV, for example, lists numerous sexual behavior disorders along with their characteristics and possible underlying mechanisms (American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition. Washington, DC, American Psychiatric Association, 1994, section 302.71, pages 496-497, of record). The psychiatric disorders that appear most-similar to "impaired social activity linked to sexuality," as discussed in the instant Specification, may be the genus of Hypoactive Sexual Desire Disorders.

These distinctly human disorders are characterized by a decreased sexual interest that is not due to physiological factors. There is no discussion in the DSM-IV of "impaired social activity" in the context of disorders of sexual interest. The Diagnostic and Statistical Manual of Mental Disorders chapter on Sexual and Gender Identity Disorders lists 20-30 disorders and subtypes. The examiner cannot determine what disorder is being treated by the instant invention, but it is probably not well-modeled by normal rats.

Applicants are also not enabled for additional routes of administration besides parenteral administration, and perhaps nasal. The arguments against *oral* administration of peptides (as presented in previous Office Actions) have not been overcome. Peptides are almost certainly *digested* when administered orally (Pontiroli, A.E., Adv. Drug Deliv. Rev, 1998, 29: 81-87, abstract, of record). Likewise, proteases abound in many tissues (Gee, et al, 1985, Biochem., 228: 119-126, of record). Treatment methods that are complex or not well-established must be worked out more-or-less completely at the time of filing of a patent application. Claiming routes of administration that have been shown to be largely ineffective with peptides, and then not describing sufficient details- such as doses, solvents, carriers, etc- indicates that significant experimentation must be undertaken to enable these methods. Routes of administration can have a dramatic effect on drug disposition, and on peptide disposition in particular (Pettit and Gombotz, 1998, TIBTECH, 16: 343-349, Table 1, of record). These examples and others illustrate that the route of administration disclosed in the instant Specification does not reasonably predict untested routes of administration.

The Response (13 November 2006) also discusses the validity of the animal model used in the inventors' experiments. There are numerous lines of evidence demonstrating that normal animals are poor models of pathologies, including the fact that there are no underlying determinants or mechanisms to correct. This was discussed at length in the Office Actions of 19 August 2005 and 11 July 2006). The examiner has made the point that many physiological and behavioral human conditions *can* be modeled in animals since many animal diseases are similar to those of human beings. For example, castration of both male rats and male humans results in a sharp drop in libido/sexual interest (Cormio, et al, 2005, International Journal of Impotence Research, 17: 23-26, of record). Thus, castrated male rats are good models for several conditions in the human male characterized by low/absent androgens. The problem in the instant Application was not whether SMR1 peptide can be used with a human endopeptidase (Response, page 8), but that normal rats were used to model a human condition of abnormal sexual behavior. Newport, et al (2002, Am. J. Psychiatry, 159(8): 1265-1283, of record) describes some characteristics of good animal models of human behavioral disorders, such as similar underlying mechanisms. It is the accuracy of the underlying determinants of a behavior that makes an animal model of human behavior most useful. The paper advises the most caution when discussing the use of animal models of psychiatric diseases (page 1267, second paragraph), stating: "Because the pathophysiology of mental disorders remains obscure, the homology of an animal model to a human psychiatric condition cannot be absolutely demonstrated." It can be assumed that a normal animal is a very poor model of a human behavioral condition, since it has no underlying pathophysiological determinants whatsoever.

Applicants also make the point that the instant Specification only presented data concerning the sexual behaviors of male rats. Therefore "the Office has provided no technical or scientific reason [ ] to doubt that corresponding social-sexual effects would be observed in female animals."

Applicant's arguments have been fully considered but they are not persuasive for the following reasons:

The examiner agrees that female rats may very well have SMR1 receptors (Response, p. 9). In addition, it is indeed unfortunate that the instant Specification does not present data concerning female sexual behaviors, other than the remark that they were made sexually receptive by administration of estrogen (Specification, p. 19). The examiner has not introduced any arguments concerning female rats and their responses to the peptide of SEQ ID NO: 2, for the simple reason that *no data exist* on the topic.

For the reasons discussed above and previously, treatment of a mental disorder by administration of SEQ ID NO: 2 is not enabled by the instant Disclosure.

Proper analysis of the Wands factors was provided in the previous Office Action. Due to: a) the large quantity of experimentation required to determine how to administer the SMR1 peptide to treat a mental disorder, a behavioral disorder, impaired social activity or a sexual disorder, b) the lack of direction or guidance in the specification regarding the same, c) the lack of working examples or evidence that associate a mental disorder or sexual disorder in humans with normal rats, d) the state of the art which acknowledges the complexity of behavioral

disorders, e) the importance of accurately mapping underlying mechanisms in an animal model of a human disease, f) the breadth of the claims which embrace methods of using the peptide to treat human conditions, and, g) use of untested routes of administration -undue experimentation would be required of the skilled artisan to make and use the claimed invention.

Claim Rejections- 35 USC § 112, second paragraph

The rejection of Claims 15 and 51 for reciting indefinite claim language is *maintained.* One skilled in the art cannot determine the metes and bounds of the claimed invention because it is not clear what the phrases "impaired social activity" and activity "linked to sexuality" mean in the context of the instant Specification. Both "impaired social activity" and activity "linked to sexuality" are poorly defined in the art, and their relationship to each other in the claims is indefinite. Furthermore, "impaired social activity linked to sexuality" disorders are poorly defined in the Specification or appear to encompass many genera of diseases and disorders, including physiological (pages 14-17). Applicants have argued (page 6, 19 April 2006) that "one skilled in the psychiatric or psychological arts would readily understand" what is meant by the disorders encompassed by the claims. However, the disorders must be named using language that is typical of one skilled in the psychiatric arts, so that it can be determined exactly which treatments are being claimed. As mentioned previously by the examiner (11 July 2006) an example of such a disorder from the DSM-III or DSM-IV would help define the genus of disorders to which the applicants are referring.

Conclusion

No claims are allowed.

Advisory information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sandra Wegert whose telephone number is (571) 272-0895. The examiner can normally be reached Monday - Friday from 9:00 AM to 5:00 PM (Eastern Time). If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Brenda Brumback, can be reached at (571) 272-0961.

The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SLW
25 April 2007

Eileen B. O'Hara

EILEEN B. O'HARA
PRIMARY EXAMINER